

**REMARKS**

By this amendment applicants delete claims 118 -167. Therefore, claims 66-117 and 332-349 are all the claims pending in the application.

Figs. 3, 7-9 have been objected to.

The Specification and the abstract have been objected to.

Claims 81 and 107 have been objected to because of certain informalities.

Claims 92-117 and 341-349 have been rejected under 35 U.S.C. § 112, first paragraph.

Claims 66-117 and 332-249 have been rejected under 35 U.S.C. § 112, second paragraph.

Claims 92-94, 97, 100, 114, 341-343, and 346 are rejected under 35 U.S.C. 103(a) as being unpatentable over WICHMANN et al. in view of Thomas (5,869,673).

Claims 92-96, 100 and 341-344 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleim in view of Thomas (5,869,673).

The Applicants traverse the rejections and request reconsideration.

***Formal Matters***

The Examiner incorrectly notes that an IDS was not filed in this case. An IDS, was in fact filed on July 8, 2003 with the same Form 1449 as was used in the parent application. It should be noted that since this is a divisional application, a second copy of each reference that was submitted in the parent is not required to be submitted in the present case. Only a form 1449 is required to be submitted.

***Objections to the drawings***

Revised Figs. 3, 7, 8A-B and 9A-B are included. In the Office Action, the Examiner refers to Fig. 2 as being objected. However, the mentioned objections should refer to Fig. 3 instead. The specification has been amended to refer to platelets as “Plt” to make it consistent with the revised Fig. 3. Further, the specification has been amended to include descriptions for Figs. 8 and 9 corresponding to the newly revised figures. Note that these descriptions are the same as the ones in the original Figs. 8 and 9 and no new matter is added.

***Rejections under section 112, first paragraph***

Claims 92-117 and 341-349 have been rejected under 35 U.S.C. § 112, first paragraph as containing new matter. Specifically the Examiner alleges that modeling for a “human” patient is not disclosed. The Applicants respectfully submit that a skilled artisan reading the specification will know that the modeling related to thrombopoiesis clearly refers to a human patient. At least the following passages from the specification clearly lead a skilled artisan to such a determination.

Recently, a Thrombopoiesis-controlling cytokine, Thrombopoietin (TPO), was isolated and its **human** recombinant analog became available. A mathematical model is disclosed herein that simulated dynamics of a Thrombopoietic lineage in the bone marrow, of platelet counts in the periphery, and effects of TPO administration on the lineage and platelet counts.....Specification, page 78

The specification refers to several publications for providing additional background material that are related to human patients (For example, see specification p. 85, l. 15).

Further in reference to the MK64 compartment in the model , the Specification notes:

Additional endomitosis in MK64 compartment  
80 takes the same amount of time  $\mu$  as before.  
Megakaryocytes of greater ploidy classes have not  
been known to be encountered in **humans**. (p. 87)

Still further, with reference to the human full-length TPO being fully active and the  
incorporation of this feature in the model the specification asserts:

Recombinant **human** full-length TPO and its  
truncated form rHuMGDF are fully active  
biologically. Therefore, in our model we add  
exogenously administered recombinant protein  
to endogenously produced TPO in order to  
calculate actual TPO concentration (c).

The specification clearly notes that computer simulations were performed using the model  
to describe the changes that occur in human Thrombopoietic systems as noted below:

Reference is now made to Fig. 7, which  
is a graphical representation of the chart  
of Fig. 6, and is the most useful model  
output. **The implementation of the described  
model results in a computer simulator that  
describes the changes that occur in the  
human Thrombopoietic system** (platelet  
counts, bone marrow precursor numbers, and  
TPO concentration) over a time span that may  
last several years. The resolution of the  
simulator output is one hour ...Specification  
page 110.

In addition the following passage further indicates that human patients were a key focus of  
the model.

The simulation tool has been carefully  
tested with respect to the published

experimental results, and has proved to be well **calibrated for average human data**. Parameters may be modified relatively quickly for efficient use of the system  
...Specification page 114

Finally, the conclusory statement in the following paragraph further illustrates that human patients were a key focus of the model.

It is possible to simulate any protocol of drug administration and any hematological state of a patient, regarding his/her platelet count and number of bone marrow megakaryocytes and their precursors. The model can be adapted to many categories of patients, or healthy platelet donors. It can also be modified to fit species other than human... Specification page 115

***Rejections under section 112, second paragraph***

All the pending claims have been rejected based on section 112, second paragraph. For a speedier prosecution of the case, the Applicants respectfully remove the term “realistic” from the claims containing the term. Claims 75, 76, 101 and 102 have also been amended for other reasons noted by the Examiner.

It is believed that this will obviate the ground for rejection of the claims under 35 U.S.C. § 112, second paragraph.

***Rejections based on prior art***

In maintaining the rejection of claims 92-97, 100, 341-344 and 346, the Examiner additionally cites Thomas (US 5,879,673). However, Thomas uses the term “model” to connote something that is completely different from that used in the present invention or the primary

references Wichmann and Kliem. In Thomas, the term “model” is used to refer to an experimental setup wherein a set of actual experimental specimens are administered a treatment according to a treatment protocol and the actual results studied. There is no mention of mathematical models, computer models and/or simulations in Thomas.

A skilled artisan would know clearly that the meaning of the term model as used in the context of Thomas is completely different from the model discussed in Wichmann and Kliem. Therefore a skilled artisan would not have been motivated to combine the teachings of Thomas and that of Wichmann and Kliem at least because the former refers to physical experimental set up (which arguably is transferred to humans) and the later refers to mathematical and/or simulation models.

Further such a combination will not work because Thomas discusses actual experiments with animals whereas Wichmann and Kliem discuss mathematical/computer models.

Further, even if the teachings of Thomas are combined with Wichmann and Kliem, there is believed to be no teaching of thrombopoiesis models for humans as in the present invention as recited in claims 92 and 341.

Further it is believed that there are substantial differences between thrombopoiesis modeling for mice and modeling for humans in that it would not be obvious to generate a model for humans from alleged teachings related to a model for mice. Some of the significant differences are noted below:

1. Megakaryopoiesis additionally takes place in the spleen of mice/rats, but not in humans.
2. It is also believed that platelet release (from mature MKs) takes place in the lungs of humans, but not in the lungs of mice/rats.
3. There are significant differences in platelet production kinetics, for example, as relating to amount in the blood, size, life span, etc. As a result of this, it is believed that there will be kinetic differences in timing and duration of thrombopoiesis response to TPO/ chemotherapy administration.
4. There are significant morphological differences, especially of the MKs, including the platelet release mechanism.
5. There is believed to be a difference in the reaction of the density of TPO-receptors on the platelet surface to TPO treatment in humans while there is no such reaction documented in mice
6. There are believed to be differences in MK ploidy distribution after TPO stimulation.
7. Iron depletion was reported to occur in primates that were myelosuppressed and then treated with TPO. Such differences have not believed to be reported in mice.
8. There are differences in the timing of TPO administration that were reported preferable for best thrombopoietic support.

For at least the above reasons, it will be non-obvious to create a model for humans based on the teachings related to a model for mice.

A mathematical model of murine thrombopoiesis, as in Wichman, makes important simplifications that are argued to be applicable to mouse. Neither Thomas, nor the secondary references Wichman or Kliem, provide any suggestion that the same simplifications are applicable to humans. At least from the points noted above, it is clear that a significantly different approach would be required for humans. The Examiner appears to be ignoring this important distinction.

In fact, Kliem, notes in the abstract that "The model, however, also points at specific gaps in our knowledge about the regulation of thrombopoiesis in vivo.", thereby clearly noting that the model presented by Kleim is not even a good model of real-life murine thrombopoiesis. From the above noted distinctions, real-life human thrombopoiesis, is by definition even further away from this murine mathematical model than real-life (in vivo) murine thrombopoiesis.

The biological model of murine thrombopoiesis is at best an early step for learning various physiological aspects of this process. At best, molecular structures of relevant molecules, binding interactions between molecules in the thrombopoiesis system, signal transduction pathways and some other general principles may be learnt. Yet, when a mathematical model of the human system as a whole is generated and used for performing predictions and making suggestions, all of the differences between murine and human thrombopoiesis need to be considered. Platelets' size, life span, production site, blood count as well as megakaryocyte ploidy distribution, etc are significantly different. Differences in the layout of the thrombopoiesis process, and in addition, in the pharmacokinetics of TPO and chemotherapeutic drugs in mice vs. humans, lead to significant differences in the kinetics of the

systems in response to pathological scenarios and/or medical treatments. Hence, human mathematical models of thrombopoiesis are distinct and non-obvious from murine models. The biomedical manifestation needs to be accurately defined (requiring expertise in both human and murine thrombopoiesis); these differences need to be translated into new mathematical formulae that require bio-mathematical expertise and additional mathematical expertise in inputting these additional formulae into the murine mathematical model.

Claims 93-97, 100, 342-344 and 347 are dependant on claims 92 and 341 and are patentable at least for the same reasons.

**CONCLUSION**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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